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(54) Aminoglycoside derivatives, processes for their production, pharmaceutical compositions containing them and such derivatives for use as pharmaceuticals.

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K.L. RINEHART et al.: "AMINOCYCLITOL ANTIBIOTICS, ACS Symposium Series 125, American Chemical Society, 1980, WASHINGTON D.C. (US), pages 1-11 "An introduction"

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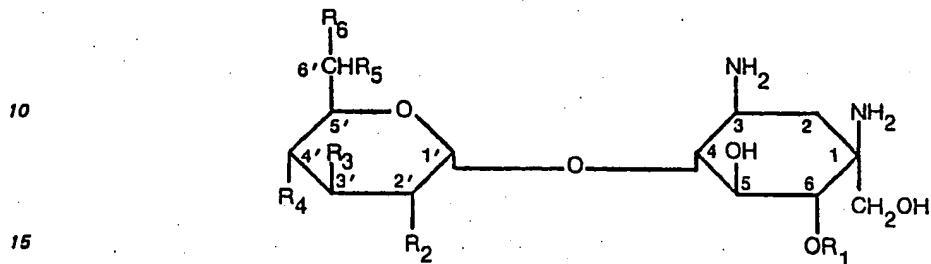
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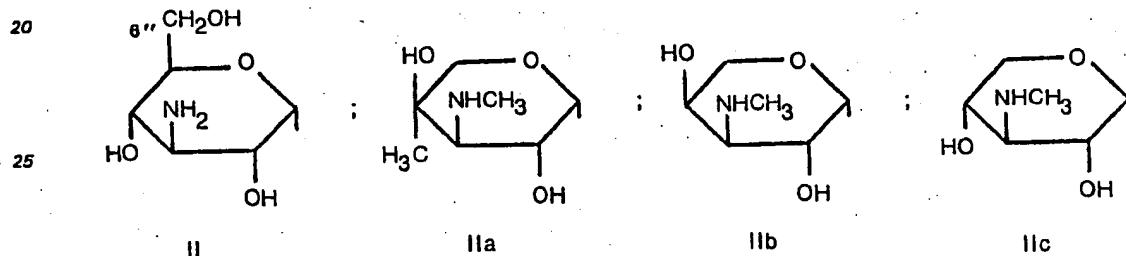
Description

The present invention concerns aminoglycoside derivatives processes for their production, pharmaceutical compositions containing them and such derivatives for use as pharmaceuticals.

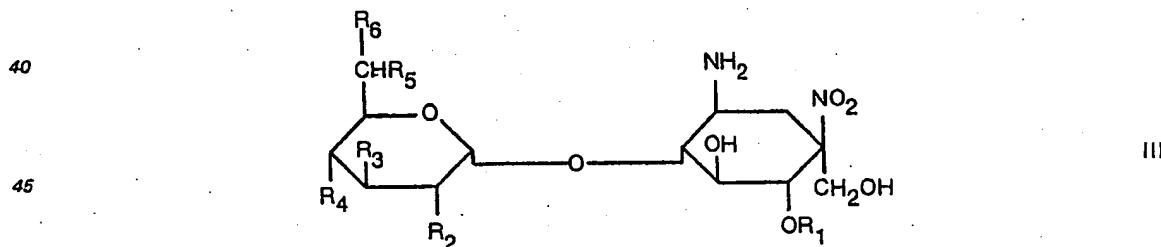
5 In particular the invention concerns compounds of formula I



wherein R₁ represents hydrogen or a group of formula



30 R₂ represents hydroxy or amino,
R₃ represents hydrogen or hydroxy,
R₄ represents hydrogen or hydroxy,
R₅ represents amino, methylamino, dimethylamino or, when R₂ represents amino also hydroxy and
R₆ represents hydrogen or methyl in free base form or in the form of an acid addition salt.
35 According to the invention these compounds can be prepared
a) by reducing a compound of formula III



40 wherein R₁ to R₆ are as defined above, and amino groups, where present, may be protected, and if required
50 deprotecting any protected amino groups still present in the compound thus obtained, or
b) to produce a compound wherein R₅ represents methylamino or dimethylamino, mono- or di-methylating a corresponding compound of formula I wherein R₅ represents amino or mono-methylating a corresponding compound wherein R₅ represents methylamino, whereby other amino groups, where present may be protected, and if required deprotecting any protected amino groups in the compound thus obtained; and recovering the compound of formula I thus obtained in free form or in the form of an acid addition salt as required.

55 Process a) can be carried out in a manner conventional for such reductions such as described in Houben-Weyl Bd. 4/Ic, for example, using Raney-Nickel and hydrogen in an inert solvent such as an alcohol e.g. methanol. Raised pressure can be advantageous.
60 Process b) can be effected using conventional methylating agents. For example for introduction of a single methyl group in a compound containing a 6'-NH₂ group this is first reacted selectively with a carbonic acid derivative of formula X—COOR₇, wherein X represents a reactive group and R₇ represents alkyl or aralkyl to produce the corresponding NHCOOR₇ derivative which is then reduced in conventional manner, e.g. with a complex metal hydride e.g. LiAlH₄. Introduction of two methyl groups in compounds
65 containing a 6'-NH₂ group can for example be carried out by protecting all amino groups except that at 6',

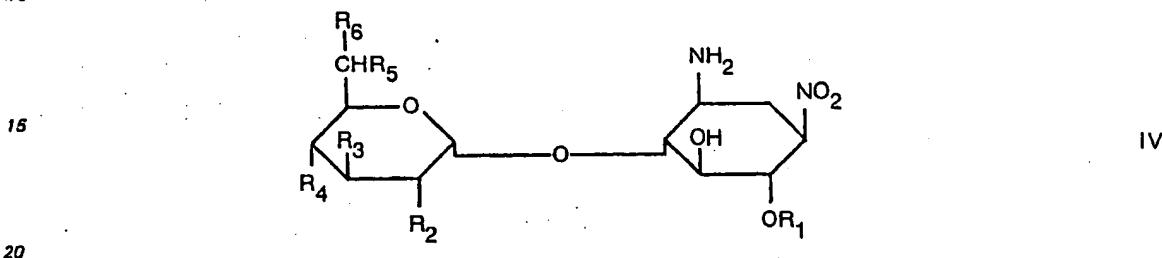
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introducing methyl groups in conventional manner e.g. by reaction with formaldehyde in the presence of a reducing agent or of NaH_2PO_3 and then deprotecting the end product. Introduction of a further methyl group in a 6'-methylamino compound may be effected analogously in conventional manner.

5 Suitable protecting groups are for example benzylloxycarbonyl, tert.butoxycarbonyl or trichlorethoxycarbonyl. These groups can be introduced and removed in conventional manner such as for example analogously to the methods described hereinafter in the examples.

The compounds of the formula I may be converted in conventional manner into their acid addition salts and vice versa.

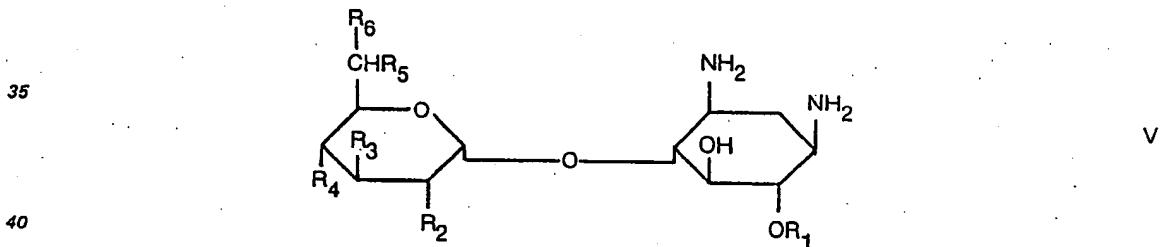
10 The starting materials of formula III can be prepared by reacting a compound of formula IV



20 wherein R_1 to R_6 are as defined above,
amino groups being optionally protected, with formaldehyde and if required deprotecting any protected amino groups in the compound thus obtained.

25 This reaction may be carried out in conventional manner in a solvent inert under the reaction conditions e.g. a lower alcohol such as methanol or a chlorinated hydrocarbon such as chloroform and in the presence of a base such as a tertiary amine e.g. triethylamine. Temperatures conveniently lie between room temperature and the boiling point of the reaction mixture. The compounds thus obtained can, of course, be further reacted directly e.g. in situ according to process a). Direct further reaction is preferred.

30 The compounds of formula IV can be obtained by oxidising a compound of formula V



35 wherein R_1 to R_6 are as defined above,
and all amino groups, with the exception of that in position 1, are protected. This oxidation can take place in conventional manner e.g. as described in J. Org. Chem. 44/659 (1979) or with KMnO_4 . Once again the resulting products may optionally be deprotected or, preferably, directly reacted further to compounds of formula III.

40 The compounds of the formula V are known, can be obtained as referred to in the literature (cf. Merck Index 4th Edition, pp. 565 and 692) or are available commercially. They can be employed in the form of mixtures such as those obtained when preparation is by fermentative methods (e.g. gentamicin C₂/C_{2a}—4/1 to 3/2). Reaction of these compounds will lead in turn to mixtures of compounds IV, III or I respectively. Such mixtures can be separated into their individual components at any stage of the preparative chain, but this is preferably carried out on deprotected end products of formula I. The methods employed in separation are conventional such as described in USP 3,984,395 or K. Byrne et. al. J. Chromatogr. 131/191 (1977).

45 The compounds of formulae III and IV are new and the former also form part of the invention.
All intermediate and end products can be isolated and purified according to known methods.

50 The compounds of formula I possess chemotherapeutic, in particular antimicrobial activity as indicated in vitro in series dilution tests and in vivo in tests on mice using various bacterial strains such as e.g. Staph. aureus, Staph. epidermidis, Haemophilus spp., Pseudomonas aeruginosa, E. coli, Proteus vulgaris, proteus mirabilis, Proteus morganii, Enterobacter cloacae, Klebsiella pneumoniae and Serratia marcescens. This activity is observed in vitro at concentrations between ca. 0.05 to 50 $\mu\text{g}/\text{ml}$ and in vivo at between ca. 0.4 and 100 mg/kg animal body weight. They are particularly effective in aminoglycoside resistant strains and have thus a broad spectrum of activity.

55 The compounds are thus indicated for use as anti-bacterially active antibiotics.

0 072 351

An indicated suitable daily dosage for use as anti-bacterially active antibiotic is from about 0.1 to 2 g. If desired this may be administered in divided doses 2 to 4 times a day in unit dosage form containing about 25 to 1500 mg of the compound or in sustained release form.

- The compounds may be used in free base form or in the form of chemotherapeutically acceptable acid addition salts e.g. as the penta hydrochloride. Such salt forms exhibit the same order of activity as the free base forms.

The compounds may be admixed with conventional chemotherapeutically acceptable diluents and carriers, and, optionally, other excipients and administered in such forms as tablets, capsules or injectable preparations.

- Such compositions also form part of the invention.

The invention therefore also concerns a method of combatting bacteria comprising administering to a subject in need of such treatment an effective amount of a compound of formula I or a chemotherapeutically acceptable acid addition salt thereof and such compounds for use as chemotherapeutic agents, in particular anti-bacterially active antibiotics.

- Preferred meanings for the substituents are

- R₁ = a) formula IIa
b) formula II
R₂ = a) hydroxy or amino
b) amino
R₃+R₄ = a) hydrogen
b) hydroxy
R₅ = a) amino, methylamino, dimethylamino
b) amino or when R₂ represents amino also hydroxy
R₆ = a) hydrogen or amino
b) hydrogen; as well as combinations of these

- A particular group of compounds according to the invention is that wherein

- R₁ represents a group of formula IIa,
R₂ represents amino,
R₃ and R₄ represent hydrogen and
R₆ represent hydrogen or methyl and
R₅ represents amino, methylamino or dimethylamino.
Another interesting group covers those compounds wherein
R₁ represents a group of formula II,
R₂ represents hydroxy or amino,
R₃ and R₄ represent hydroxy,
R₅ represents amino or when R₂ represents amino also hydroxy and
R₆ represents hydrogen.

- A particularly preferred single compound is 1-C-hydroxymethylgentamicin C₂ in free base form or acid addition salt form preferably pentahydrochloride or sulfate salt form.

- The following examples illustrate the invention. All temperatures are in degrees centigrade.

Example 1

- 1-C-Hydroxymethylgentamicin C₂, Pentahydrochloride (compound no. 1 — process a))
0.64 g of 3,2',6',3''-Tetra-N-tert.-butoxycarbonyl-1-desamino-1-nitrogentamicin C₂ are dissolved in
50 5 ml of methanol and after cooling to -7° reacted with 0.3 ml of triethylamine. After 5 mins the solution is poured into 10 ml of 37% formaldehyde solution and raised to room temperature. After dilution with water and acidification with 0.1 N HCl the solution is extracted with dichloromethane and the organic phase concentrated on a rotary evaporator. The substance having R_f = 0.56 (in dichloromethane/methanol = 10/1) is isolated by chromatography on silica gel with dichloromethane/methanol (100/2—4). The resulting compound is reduced with hydrogen at 4 atm. using a Raney-Nickel suspension in 20 ml of methanol. After filtration of the catalyst the solution is concentrated on a rotary evaporator and the residue taken up with ethyl acetate, washed with 2N ammonia solution and concentrated on a rotary evaporator. This residue is taken up in 5 ml of trifluoroacetic acid and mixed after 3 minutes with 100 ml of diethylether. The precipitate is filtered off and converted to the (penta)hydrochloride using Amberlite® IRA 401 S ion exchange resin, R_f = 0.53 (dichloromethane/methanol/25% ammonia = 2/2/1).
C—13 NMR: 102, 8; 96, 0; 85, 8; 78, 0; 73, 2; 70, 7; 69, 8; 68, 9; 67, 0; 64, 1; 60, 7; 59, 3; 50, 4; 49, 6; 48, 2; 35, 2; 29, 8; 23, 0; 21, 7; 21, 2; 13, 5.

0 072 351

Example 2

1-C-Hydroxymethylgentamicin C_{1a}.Pentahydrochloride (compound No. 2 — process a)

5 0.8 g of 3,2',6',3''-Tetra-N-tert.-butoxycarbonyl-1-desamino-1-nitrogentamicin C_{1a} are dissolved in 20 ml of chloroform, reacted with 10 g of paraformaldehyde and 1 ml of triethylamine and refluxed for 30 minutes. The resulting mixture is filtered under suction and the mother liquor chromatographed over silica gel with ethylacetate/hexane (2/1). R_f = 0.5 (in dichloromethane/methanol = 9/1). The resulting product is reduced with hydrogen at 4 atm. using a Raney-Nickel suspension in 30 ml of methanol. Filtration of the catalyst yields an anorphous foam which is dissolved in 10 ml of trifluoroacetic acid and after 7 minutes added to 200 ml of diethylether. The precipitate is filtered under suction and chromatographed over silica gel with chloroform/methanol/30% ammonia (70/26/9). The product having R_f = 0.13 in the above eluant is collected and converted by acidification with methanolic hydrochloric acid and precipitation with diethylether into the (penta)hydrochloride.

10 H—NMR, characteristic signals: 1,37 s, 3H; 2, 72 dd, J₁=14, J₂=3, 5, 1H; 2, 96 s, 3H; 5, 15 d, J=3, 6, 1H; 5, 85 d, J=3, 6, 1H.

15 Analogously to the above Examples 1 and 2 or as otherwise herein described, the following compounds may be obtained from the appropriate starting materials:

1-C-Hydroxymethylgentamicin C₁.pentahydrochloride (compound no. 3).

C—13 NMR: 103, 1; 95, 5; 86, 1; 77, 6; 73, 7; 71, 1; 70, 3; 69, 1; 67, 5; 64, 7; 61, 1; 59, 8; 58, 7; 49, 9; 48, 6; 35, 6; 32, 3; 30, 2; 24, 4; 22, 1; 21, 8; 10, 5.

20 1-C-Hydroxymethylgentamicin C_{2a}.pentahydrochloride (compound no. 4).

H—NMR, characteristic signals: 1,34 d, J=7, 3H; 1, 37 s, 3H; 2, 72 dd, J₁=13, 5, J₂=3, 5, 1H; 2, 96 s, 3H; 5, 12 d, J=3, 6, 1H; 5, 91 d, J=3, 6, 1H.

1-C-Hydroxymethylgentamicin C₁.pentahydrochloride (compound no. 5).

1-C-Hydroxymethylgentamicin C₂/C_{2a}.pentahydrochloride (compound no. 6).

25 Compound no. 6 is obtained from starting materials themselves derived from fermentatively produced gentamicin C₂/C_{2a} (ca 4/1) and can be resolved as follows:

30 300 mg of 1-C-Hydroxymethylgentamicin C₂/C_{2a}.pentahydrochloride are dissolved in water and this solution introduced onto a middle pressure column (1.5 m × 1.6 cm) filled with CG 50 l ion exchange resin (NH₄⁺-form). Elution with ca 1 litre of water follows (flow 20 ml/minute, pressure 4—5 bar). This is followed by gradient elution over 90 minutes from water to 0.4 N ammonia. The fractions containing the product are concentrated individually on a rotary evaporator. The first 5 fractions contain according to 250 MHz H—NMR the desired C₂ derivative in 95% purity.

Example 3

1-C-Hydroxymethyl-6'-N-methylgentamicin C_{1a}.pentahydrochloride (compound no. 7 — process b)

35 1.63 g of 1-C-Hydroxymethylgentamicin C_{1a} (free base) are dissolved in 30 ml of methanol and a solution of 1.06 g of N-benzyloxycarbonyloxy)-5-norbornene-2,3-dicarboxylic acid imide in 20 ml of methanol and 5 ml of dichloro-methane added at -20°. After 1 hour the mixture is concentrated on a rotary evaporator and the residue chromatographed on silica gel with chloroform/methanol/25% ammonia (15/4/1). The product with R_f = 0.45 (in chloroform/methanol/30% ammonia = 70/21/9) is collected. 250 mg of the 1-C-hydroxymethyl-6'-carbobenzoxygentamicin C_{1a} thus obtained are dissolved in 25 ml of abs. tetrahydrofuran and under an argon atmosphere lithium aluminium hydride added until gas evolution ceases. The mixture is then refluxed for 1 h. The excess reducing agent is destroyed with methanol and the reaction mixture acidified with acetic acid, the precipitate filtered off and the clear filtrate concentrated on a rotary evaporator. The residue is dissolved in 10 ml of water and then eluted over CG 50 l ion exchange resin (NH₄⁺-form) initially with water and then gradually with water to 0.5 N ammonia.

The fractions containing the product are concentrated, the residue dissolved in methanolic hydrochloric acid and the title product precipitated with diethylether. R_f = 0.2 (in chloroform/methanol/30% ammonia = 70/26/9).

50 H—NMR, characteristic signals: 1, 35 s, 3H; 2, 70 dd, J₁=14, J₂=3, 5, 1H; 2, 78 s, 3H; 2, 95 s, 3H; 5, 12 d, J=3, 6, 1H; 5, 84 d, J=3, 6, 1H.

Example 4

1-C-Hydroxymethyl-6'-N-dimethylgentamicin C_{1a}.sulphate (compound 8 — process b)

55 400 mg 1-Hydroxymethyl-6'-carbobenzoxygentamicin C_{1a} are dissolved in 10 ml of methanol and 900 mg of di-tert.-butyldicarbonate and 0.2 ml of pyridine added. The mixture is stirred for 2 days at room temperature and then refluxed for 3 hrs. Concentration on a rotary evaporator is carried out followed by dissolution of the residue in diethylether and threefold trituration with 2 N ammonia. The organic phase is concentrated, dissolved in 10 ml of methanol, mixed with 500 mg of ammonium formate, 2 ml of water and 100 mg palladium 10% on charcoal and refluxed for 15 minutes. Extraction by shaking with water and ethylacetate follows and the resulting ethylacetate phase is dried and concentrated. The residue is dissolved in 10 ml dioxane, 10 ml of 1 N sodium dihydrogen phosphite solution and 3 ml of 33% formaldehyde solution added and the mixture warmed for 30 minutes at 65°. The pH is then adjusted to 11 with 1 N sodium hydroxide and extraction with chloroform is carried out three times.

60 The organic phase is dried and concentrated on a rotary evaporator and the residue dissolved in 5 ml of trifluoroacetic acid, mixed after 7 minutes with 100 ml of diethyl ether and the precipitate filtered off

0 072 351

under suction and washed with ether. The product is dissolved in 5 ml of water and converted to the sulphate in a column with Amberlite® IRA 401 S ion exchange resin (sulphate-form). $R_f = 0.30$ (in chloroform/methanol/30% ammonia = 70/26/9).

5. H-NMR, characteristic signals: 1, 38 s, 3H; 2, 7 dd, $J_1=14$, $J_2=3, 5$, 1H; 2, 97 s, 3H; 2, 99 s, 6H; 5, 18 d, $J=3, 6$, 1H; 5, 88 d, $J=3, 6$, 1H.

The required starting materials are prepared as follows:

A) 3,2',6',3"-Tetra-N-tert.-butoxycarbonyl-1-desamino-1-nitrogentamicin C₂ (for example 1)

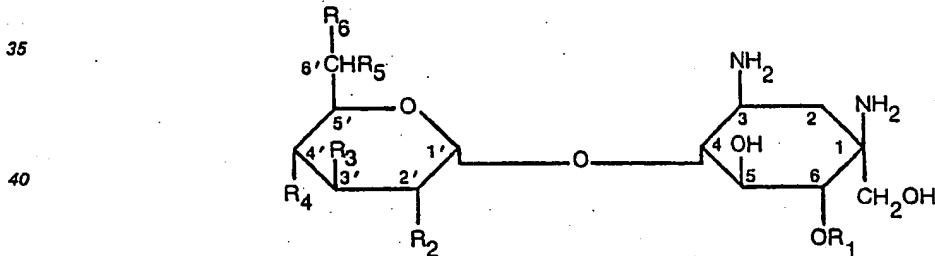
10. To a solution of 17 g of 3,2',6',3"-tetra-N-tert.-butoxycarbonylgentamicin C₂ and 3.4 g 3-tert.-butyl-4-hydroxy-5-methylenephenoxyphenylsulphide in 750 ml of 1,2-dichloroethane are added whilst boiling 34 g of 3-chloroperbenzoic acid in solid form. After 30 minutes the solution is concentrated on a rotary evaporator and the residue triturated with 20% KHSO₄, saturated NaHCO₃ and water and chromatographed over silica gel (ethylacetate/hexane = 3/2). The substance with $R_f=0.17$ (dichloromethane/methanol = 20/1) is isolated.

15. B) 3,2',6',3"-Tetra-N-tert.-butoxycarbonyl-1-desamino-1-nitrogentamicin C_{1a} (for example 2)
A mixture of 50 g potassium permanganate and 125 g potassium dihydrogenphosphate in 0.5 litre of water is brought to 75° and 25 g of 3,2',6',3"-tetra-N-tert.-butoxycarbonylgentamicin C_{1a} dissolved in 0.5 litre of acetone added in one gush. The mixture is refluxed for 3 minutes and poured into ice-water containing 150 g of sodium hydrogensulphite. The manganese dioxide is filtered off and the solution extracted with chloroform. After drying, the organic phase is concentrated on a rotary evaporator and the residue chromatographed over silica gel with ethylacetate/hexane = 3/2. A colourless foam is obtained. $R_f = 0.16$ (dichloromethane/methanol = 20/1).

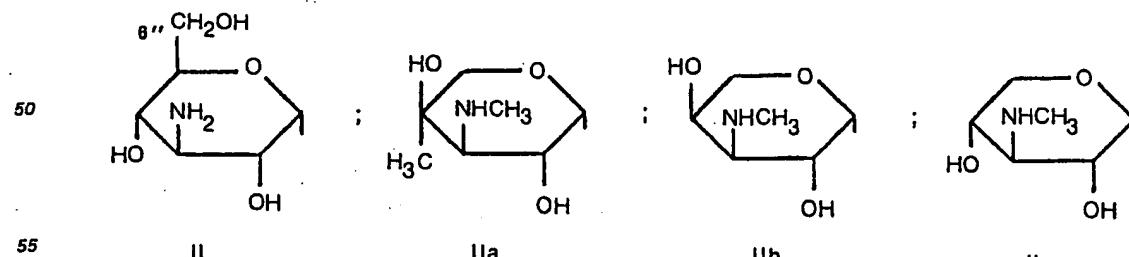
25. The following compounds may be obtained analogously:
3,2',6',3"-Tetra-N-tert.-butoxycarbonyl-1-desamino-1-nitrogentamicin C₁. $R_f = 0.74$ (dichloromethane/methanol = 9/1).
3,2',6',3"-Tetra-N-tert.-butoxycarbonyl-1-desamino-1-nitrogentamicin C_{2a}. $R_f = 0.17$ (dichloromethane/methanol = 20/1)

30. Claims for the Contracting States: BE CH DE FR GB IT LI LU NL SE

1. Compounds of formula I

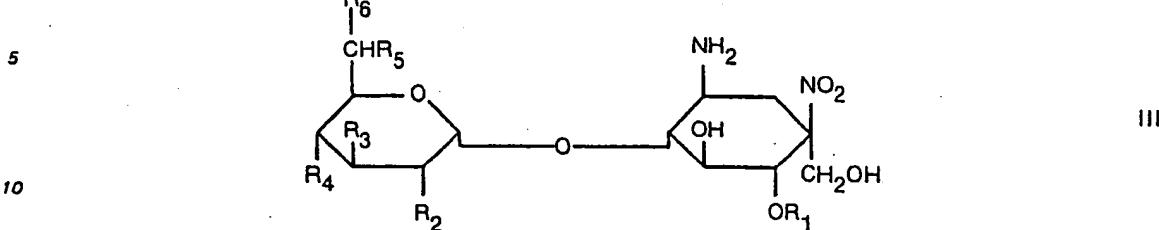


45. wherein R₁ represents hydrogen or a group of formula



55. R₂ represents hydroxy or amino,
R₃ represents hydrogen or hydroxy,
R₄ represents hydrogen or hydroxy,
R₅ represents amino, methylamino, dimethylamino or, when R₂ represents amino also hydroxy and
R₆ represents hydrogen or methyl in free base form or in the form of an acid addition salt.
60. 2. 1-C-Hydroxymethylgentamicin C₂ in free base form or in the form of an acid addition salt.
3. A compound according to Claim 2 in the form of its pentahydrochloride or sulphate.
65. 4. A process for preparing a compound as claimed in any one of Claims 1 to 3 which comprises:

a) reducing a compound of formula III



wherein R₁ to R₆ are as defined above, and amino groups, where present, may be protected, and if required deprotecting any protected amino groups still present in the compound thus obtained, or

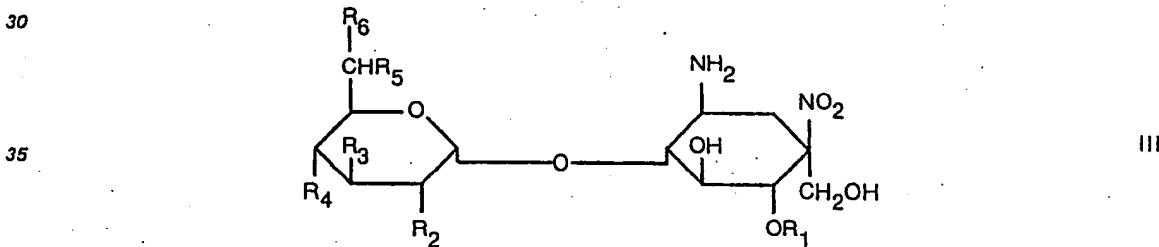
15 b) to produce a compound wherein R₅ represents methylamino or dimethylamino, mono- or di-methylating a corresponding compound of formula I wherein R₅ represents amino or mono-methylating a corresponding compound wherein R₅ represents methylamino, whereby other amino groups, where present may be protected, and if required deprotecting any protected amino groups in the compound thus obtained; and recovering the compound of formula I thus obtained in free form or in the form of an acid addition salt as required.

20 5. A pharmaceutical composition comprising a compound of formula I as claimed in Claim 1 or a chemotherapeutically acceptable salt thereof together with a chemotherapeutically acceptable diluent or carrier.

25 6. A compound of formula I as claimed in Claim 1 or a chemotherapeutically acceptable salt thereof for use as a pharmaceutical.

7. A compound of formula I as claimed in Claim 1 or a chemotherapeutically acceptable salt thereof for use as an anti-bacterially active antibiotic.

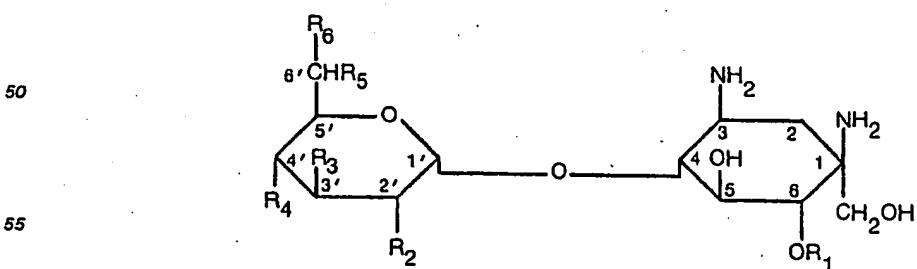
8. Compounds of formula III



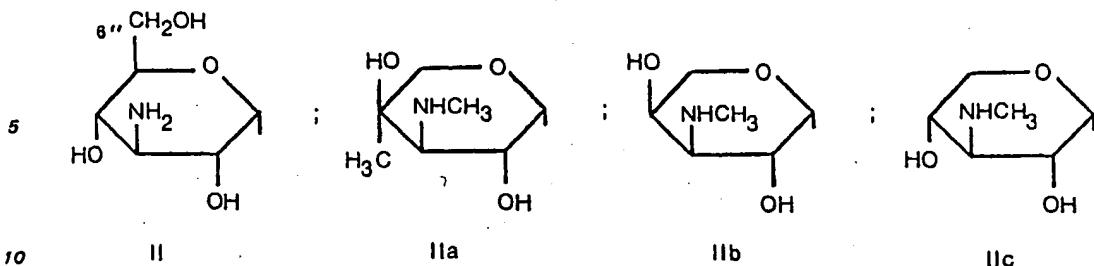
40 wherein R₁ to R₆ are as defined in claim 1.

Claims for the Contracting State: AT

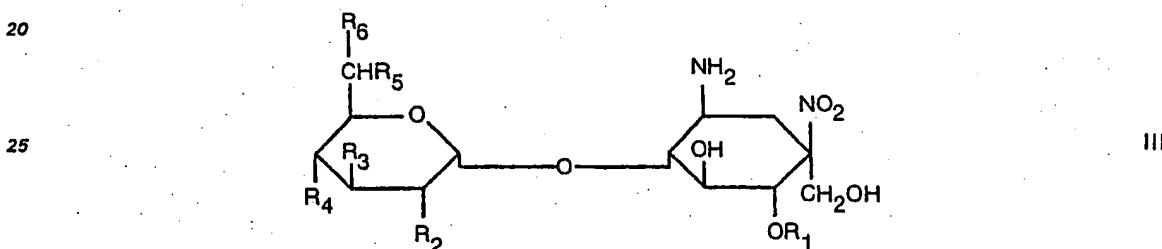
1. A process for preparing a compound of formula I



60 wherein R₁ represents hydrogen or a group of formula



*R*₂ represents hydroxy or amino,
*R*₃ represents hydrogen or hydroxy,
*R*₄ represents hydrogen or hydroxy,
15 *R*₅ represents amino, methylamino, dimethylamino or, when *R*₂ represents amino also hydroxy and
 *R*₆ represents hydrogen or methyl in free base form or in the form of an acid addition salt, which
comprises:
a) reducing a compound of formula III



30 wherein R_1 to R_6 are as defined above, and amino groups, where present, may be protected, and if required deprotecting any protected amino groups still present in the compound thus obtained, or
35 b) to produce a compound wherein R_5 represents methylamino or dimethylamino, mono- or di-methylating a corresponding compound of formula I wherein R_5 represents amino or mono-methylating a corresponding compound wherein R_5 represents methylamino, whereby other amino groups, where present may be protected, and if required deprotecting any protected amino groups in the compound thus obtained; and recovering the compound of formula I thus obtained in free form or in the form of an acid addition salt as required.

40 2. A process as claimed in Claim 1 wherein the compound prepared is 1-C-hydroxymethylgentamicin C2 in free base form or in the form of an acid addition salt.

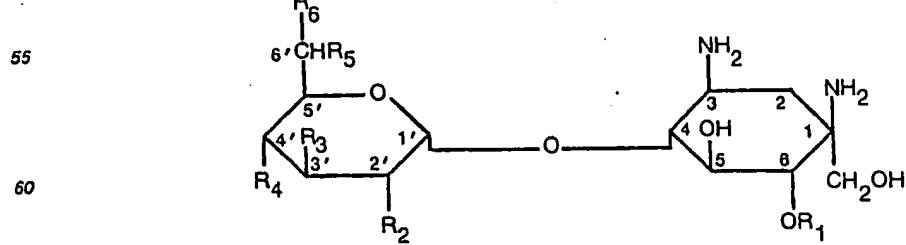
3. A process as claimed in Claim 2 wherein the acid addition salt form is the pentahydrochloride or sulphate.

4. A pharmaceutical composition comprising a compound prepared according to any one of Claims 1 to 3 in free base form or in the form of a chemotherapeutically acceptable acid addition salt thereof together with a chemotherapeutically acceptable diluent or carrier.

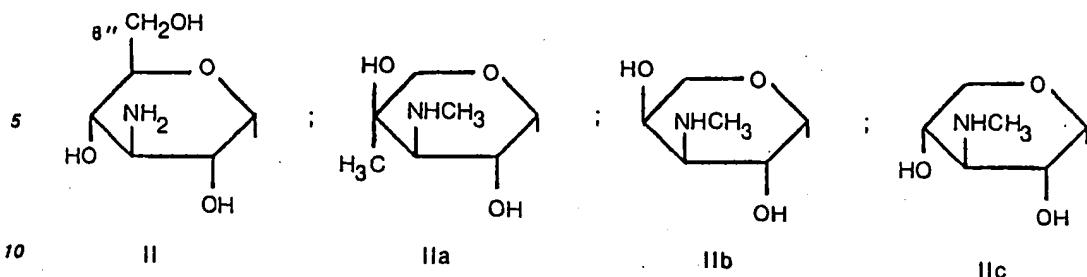
5. A compound as prepared according to any one of Claims 1 to 3 in free base form or in the form of a chemotherapeutically acceptable acid addition salt for use as a pharmaceutical.

6. A compound as prepared according to any one of Claims 1 to 3 in free base form or in the form of a chemotherapeutically acceptable acid addition salt for use as an anti-bacterially active antibiotic.

50 7. A process for the preparation of a pharmaceutical composition comprising admixing a compound of formula I



65 wherein R₁ represents hydrogen or a group of formula



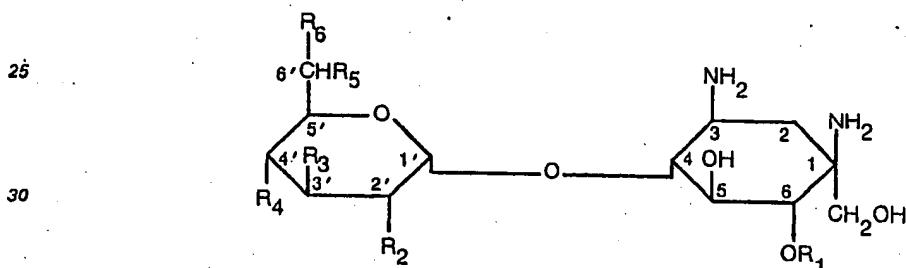
R₂ represents hydroxy or amino,
R₃ represents hydrogen or hydroxy,

R₄ represents hydrogen or hydroxy,

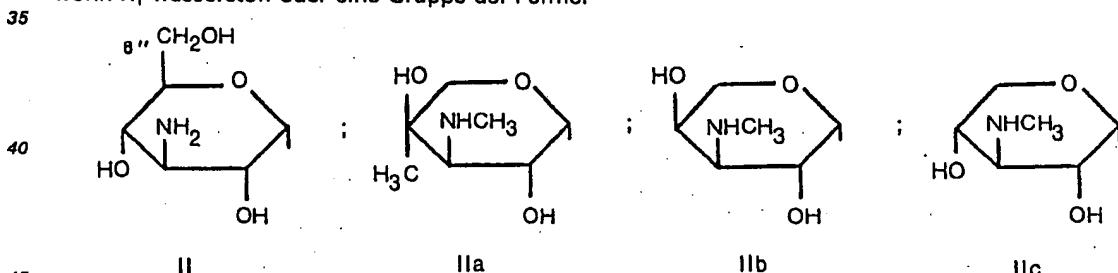
15 R₅ represents amino, methylamino, dimethylamino or, when R₂ represents amino also hydroxy and
R₆ represents hydrogen or methyl in free base form or in the form of a chemotherapeutically acceptable addition salt thereof with a chemotherapeutically acceptable diluent or carrier.

20 Patentansprüche für die Vertragsstaaten: BE CH DE FR GB IT LI LU NL SE

1. Verbindungen der Formel I



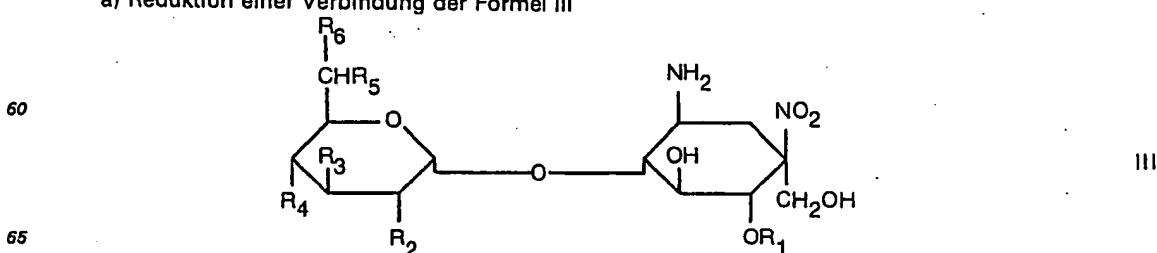
worin R₁ Wasserstoff oder eine Gruppe der Formel



45 darstellt,
R₂ Hydroxy oder Amino darstellt,
R₃ Wasserstoff oder Hydroxy darstellt,
R₄ Wasserstoff oder Hydroxy darstellt,
50 R₅ Amino, Methylamino, Dimethylamino oder, wenn R₂ Amino darstellt auch Hydroxy darstellt, und
R₆ Wasserstoff oder Methyl darstellt in Form der freien Base oder in Form eines Säureadditionssalzes.
2. 1-C-Hydroxymethylgentamicin C₂ in Form der freien Base oder in Form eines Säureadditionssalzes.
3. Eine Verbindung gemäß Anspruch 2 in Form von deren Pentahydrochlorid oder Sulfat.
4. Ein Verfahren zur Herstellung einer Verbindung wie in einem der Ansprüche 1 bis 3 beansprucht,

55 bestehend aus

a) Reduktion einer Verbindung der Formel III

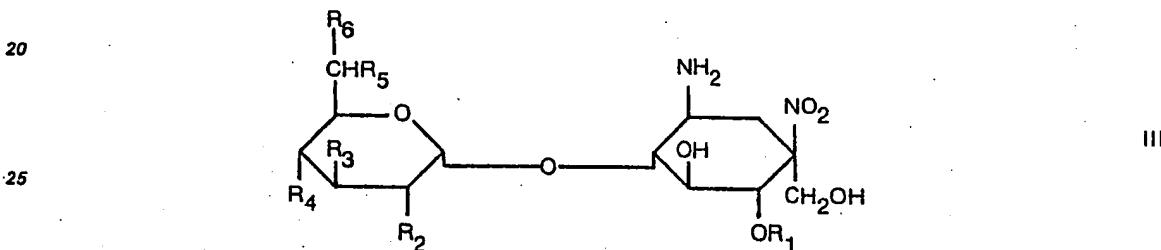


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worin R₁ bis R₆ wie oben definiert sind und Amino-Gruppen, wo vorhanden, geschützt sein können, und wenn notwendig Entschützung etwaiger geschützter Amino-Gruppen, die in der so erhaltenen Verbindung noch vorhanden sind, oder

- b) um eine Verbindung, worin R₅ Methylamino oder Dimethylamino darstellt, herzustellen, Mono- oder
 5 Dimethylierung einer entsprechenden Verbindung der Formel I worin R₅ Amino darstellt oder Mono-
 methylierung einer entsprechenden Verbindung worin R₅ Methylamino darstellt, wobei andere Amino-
 gruppen, wo vorhanden, geschützt sein können und wenn notwendig Entschützung etwaiger geschützter Amino-
 Gruppen in den so erhaltenen Verbindungen, und Gewinnung der so erhaltene Verbindung der
 Formel I in freier Form oder in Form eines Säureadditionssalzes.
- 10 5. Eine pharmazeutisch Zusammensetzung bestehend aus einer Verbindung wie im Anspruch 1
 beansprucht oder einem chemotherapeutisch annehmbaren Salz davon zusammen mit einem
 chemotherapeutisch annehmbaren Verdünner oder Träger
6. Eine Verbindung der Formel wie im Anspruch 1 beansprucht oder ein chemotherapeutisch annehm-
 bares Salz davon zur Verwendung als Pharmazeutikum.
- 15 7. Eine Verbindung der Formel I wie im Anspruch 1 beansprucht oder ein chemotherapeutisch annehm-
 bares Salz davon zur Verwendung als antibakteriell wirksames Antibiotikum.

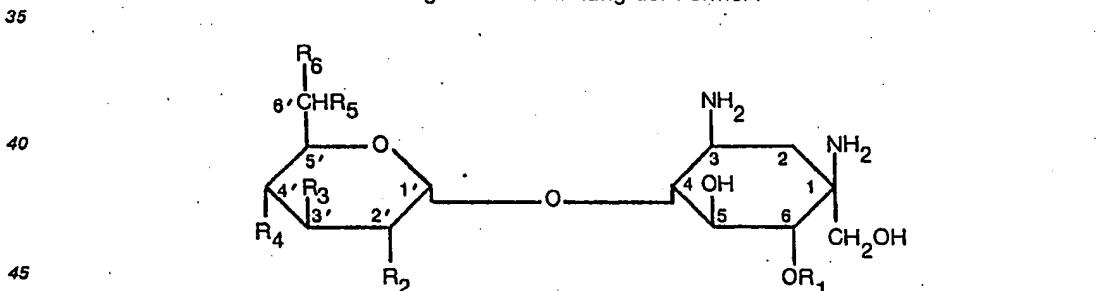
8. Verbindungen der Formel III



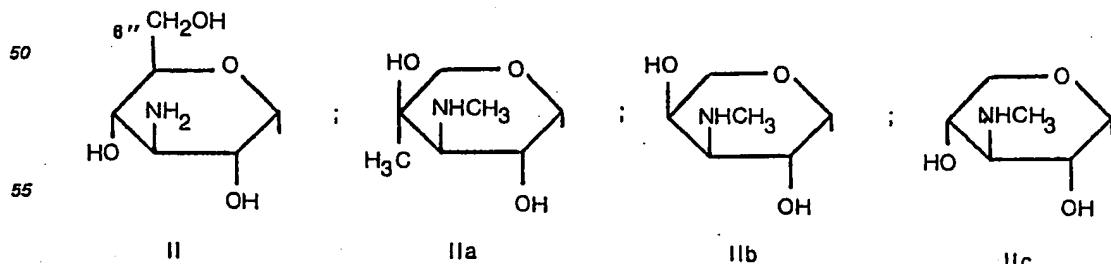
- 30 worin R₁ bis R₆ wie im Anspruch 1 definiert sind.

Patentansprüche für den Vertragsstaat: AT

1. Ein Verfahren zur Herstellung einer Verbindung der Formel I



worin R₁ Wasserstoff oder eine Gruppe der Formel

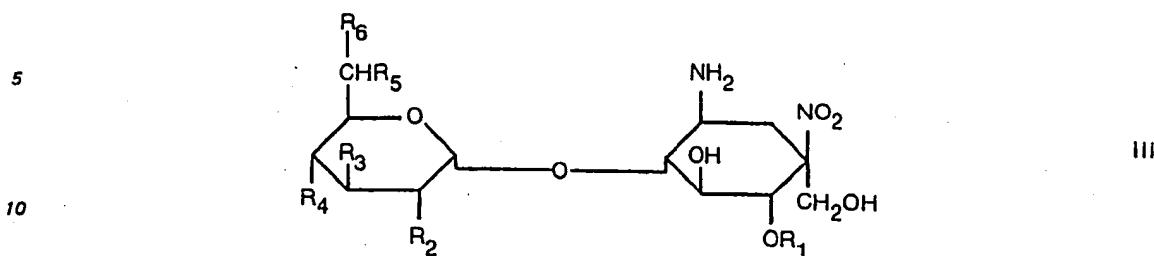


darstellt,

- 60 R₂ Wasserstoff oder Amino darstellt,
 R₃ Wasserstoff oder Hydroxy darstellt,
 R₄ Wasserstoff oder Hydroxy darstellt,
 R₅ Amino, Methylamino, Dimethylamino oder, wenn R₂ Amino darstellt auch Hydroxy darstellt, und
 R₆ Wasserstoff oder Methyl darstellt in Form der freien Base oder in Form eines Säureadditionssalzes
- 65 bestehend aus

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a) Reduktion einer Verbindung der Formel III



worin R₁ bis R₆ wie oben definiert sind und Amino-Gruppen, wo vorhanden, geschützt sein können, und wenn notwendig Entschützung etwaiger geschützter Amino-Gruppen, die in der so erhaltenen Verbindung
15 noch vorhanden sind, oder

- b) um eine Verbindung, worin R₅ Methylamino oder Dimethylamino darstellt, herzustellen, Mono- oder Dimethylierung einer entsprechenden Verbindung der Formel I worin R₅ Amino darstellt oder Monomethylierung einer entsprechenden Verbindung worin R₅ Methylamino darstellt, wobei andere Amino-
20 Gruppen, wo vorhanden, geschützt sein können und wenn notwendig Entschützung etwaiger geschützter Amino-Gruppen in den so erhaltenen Verbindungen, und Gewinnung der so erhaltene Verbindung der Formel I in freier Form oder in Form eines Säureadditionssalzes.

2. Ein Verfahren wie im Anspruch 1 beansprucht, worin die hergestellte Verbindung 1-C-Hydroxy-methylgentamicin C2 in Form der freien Base oder in Form eines Säureadditionssalzes ist.

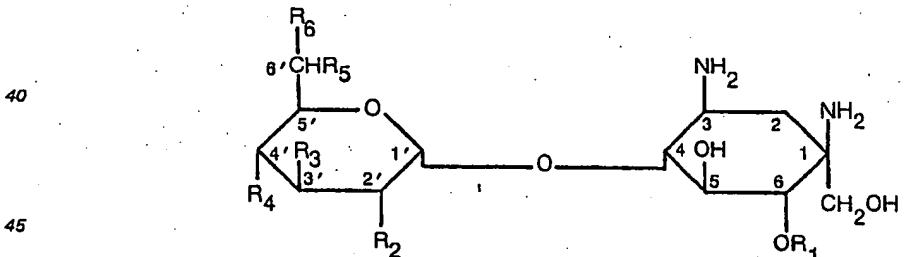
3. Ein Verfahren wie im Anspruch 1 beansprucht, worin die Säureadditionssalzform das Pentahydrochlorid oder Sulfat ist.

4. Ein pharmazeutische Zusammensetzung bestehend aus einer nach einem der Ansprüche 1 bis 3 hergestellten Verbindung in Form der freien Base oder in Form eines chemotherapeutisch annehmbaren Salzes davon zusammen mit einem chemotherapeutisch annehmbaren Verdünner oder Träger.

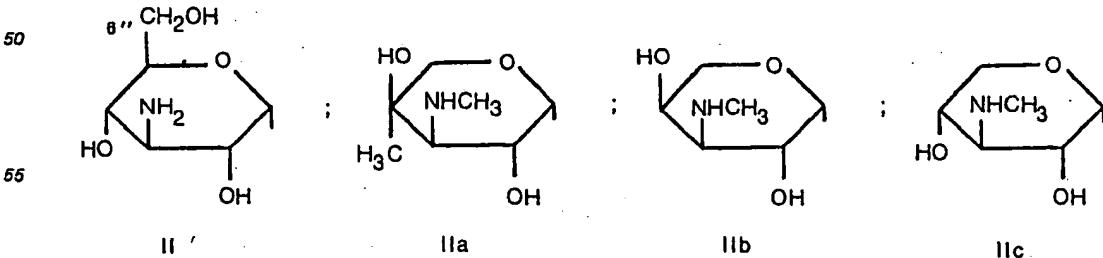
5. Eine nach einem der Ansprüche 1 bis 3 hergestellte Verbindung in Form der freien Base oder in Form eines chemotherapeutisch annehmbaren Säureadditionssalzes zur Verwendung als Pharmazeutikum.

6. Eine nach einem der Ansprüche 1 bis 3 hergestellte Verbindung in Form der freien Base oder in Form eines chemotherapeutisch annehmbaren Säureadditionssalzes zur Verwendung als antibakteriell wirksames Antibiotikum.

7. Ein Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung bestehend aus Beimischung einer Verbindung der Formel I



worin R₁ Wasserstoff oder eine Gruppe der Formel



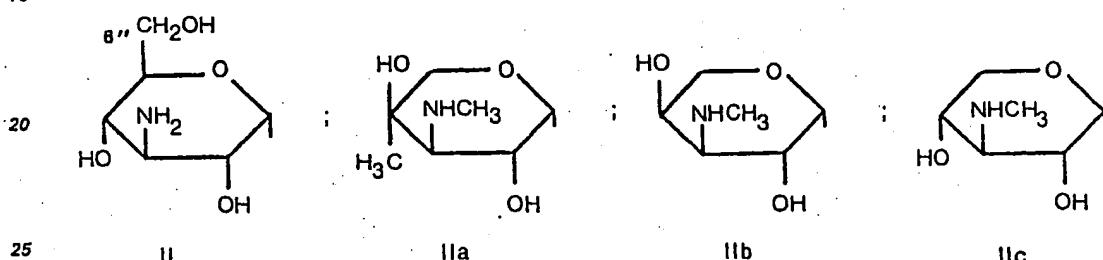
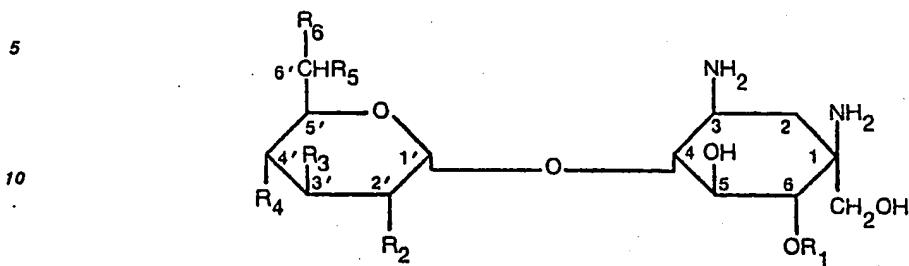
darstellt,

- 60 R₂ Wasserstoff oder Hydroxy darstellt,
R₃ Wasserstoff oder Hydroxy darstellt,
R₄ Wasserstoff oder Hydroxy darstellt,
R₅ Amino, Methylamino, Dimethylamino oder, wenn R₂ Amino darstellt auch Hydroxy darstellt, und
R₆ Wasserstoff oder Methyl darstellt in Form der freien Base oder in Form eines chemotherapeutisch annehmbaren Säureadditionssalzes mit einem chemotherapeutisch annehmbaren Verdünner oder Träger.

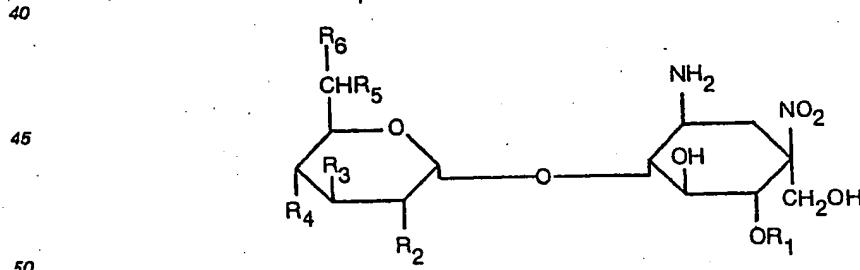
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Revendications pour les Etats contractants: BE CH DE FR GB IT LI LU NL SE

1. Les composés de formule I



- R₂ représente un groupe hydroxy ou amino,
 R₃ représente l'hydrogène ou un groupe hydroxy,
 R₄ représente l'hydrogène ou un groupe hydroxy,
 30 R₆ représente un groupe amino, méthylamino, diméthylamino ou, lorsque R₂ représente un groupe amino, également un groupe hydroxy et
 R₆ représente l'hydrogène ou un groupe méthyle, sous forme de base libre ou sous forme d'un sel d'addition d'acide.
 35 2. La 1-C-hydroxyméthylgentamicine C₂ sous forme de base libre ou sous forme d'un sel d'addition d'acide.
 3. Un composé selon la revendication 2 sous forme de son pentachlorhydrate ou sulfate.
 4. Un procédé de préparation d'un composé tel que revendiqué à l'une quelconque des revendications 1 à 3, qui comprend:
 a) la réduction d'un composé de formule III

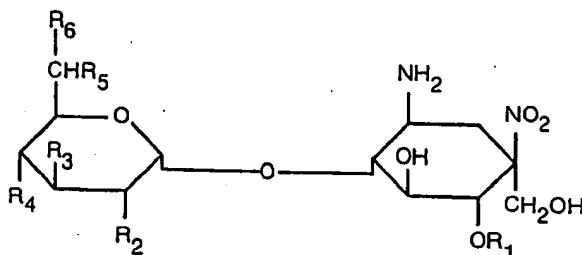


- dans laquelle R₁ à R₆ sont tels que définis ci-dessus, et des groupes amino, lorsqu'ils sont présents, peuvent être protégés, et si nécessaire la déprotection de tout groupe amino protégé encore présent dans le composé ainsi obtenu, ou
 55 b) pour préparer un composé dans lequel R₅ représente un groupe méthylamino ou diméthylamino, la mono- ou la di-méthylation d'un composé de formule I correspondant dans lequel R₆ représente un groupe amino ou la mono-méthylation d'un composé correspondant dans lequel R₆ représente un groupe méthylamino, d'autres groupes amino, lorsqu'ils sont présents, pouvant être protégés, et si nécessaire la déprotection de tout groupe amino protégé dans le composé ainsi obtenu, et la récupération du composé 60 de formule I ainsi obtenu, selon les besoins sous forme libre ou sous forme d'un sel d'addition d'acide.
 5. Une composition pharmaceutique comprenant un composé de formule I tel que revendiqué à la revendication 1 ou un sel acceptable du point de vue chimiothérapeutique de ce composé, ensemble avec un diluant ou véhicule acceptables du point de vue chimiothérapeutique.
 6. Un composé de formule I tel que revendiqué à la revendication 1 ou un sel acceptable du point de 65 vue chimiothérapeutique de ce composé, pour l'utilisation comme médicament.

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7. Un composé de formule I tel que revendiqué à la revendication 1 ou un sel acceptable du point de vue chimiothérapeutique de ce composé, pour l'utilisation comme antibiotique à activité anti-bactérienne.
 8. Les composés de formule III

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III

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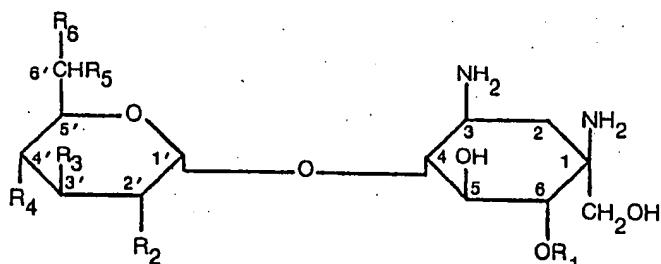
15 dans laquelle R₁ à R₆ sont tels que définis à la revendication 1.

Revendications pour l'Etat contractant: AT

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1. Un procédé de préparation d'un composé de formule I

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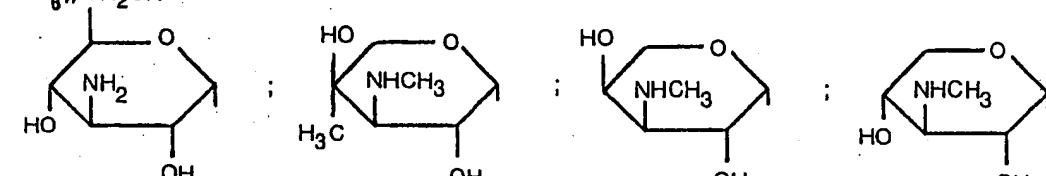
30

dans laquelle R₁ représente l'hydrogène ou un groupe de formule

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$\text{R}_6 = \text{CH}_2\text{OH}$

40



II

IIa

IIb

IIc

45

R₂ représente un groupe hydroxy ou amino,

R₃ représente l'hydrogène ou un groupe hydroxy,

R₄ représente l'hydrogène ou un groupe hydroxy,

R₅ représente un groupe amino, méthylamino, diméthylamino ou, lorsque R₂ représente un groupe

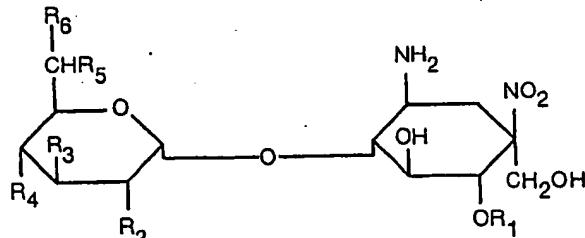
50 amino, également un groupe hydroxy et

R₆ représente l'hydrogène ou un groupe méthyle, sous forme de base libre ou sous forme d'un sel d'addition d'acide, qui comprend:

a) la réduction d'un composé de formule III

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III

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dans laquelle R₁ à R₆ sont tels que définis ci-dessus, et des groupes amino, lorsqu'ils sont présents, peuvent être protégés, et si nécessaire la déprotection de tout groupe amino protégé encore présent dans le composé ainsi obtenu, ou

5 b) pour préparer un composé dans lequel R₆ représente un groupe méthylamino ou diméthylamino, la mono- ou la di-méthylation d'un composé de formule I correspondant dans lequel R₅ représente un groupe amino ou la mono-méthylation d'un composé correspondant dans lequel R₅ représente un groupe méthylamino, d'autres groupes amino, lorsqu'ils sont présents, pouvant être protégés, et si nécessaire la déprotection de tout groupe amino protégé dans le composé ainsi obtenu, et la récupération du composé de formule I ainsi obtenu, selon les besoins sous forme libre ou sous forme d'un sel d'addition d'acide.

10 2. Un procédé tel que revendiqué à la revendication 1, dans lequel le composé préparé est la 1-C-hydroxyméthylgentamicine C₂ sous forme de base libre ou sous forme d'un sel d'addition d'acide.

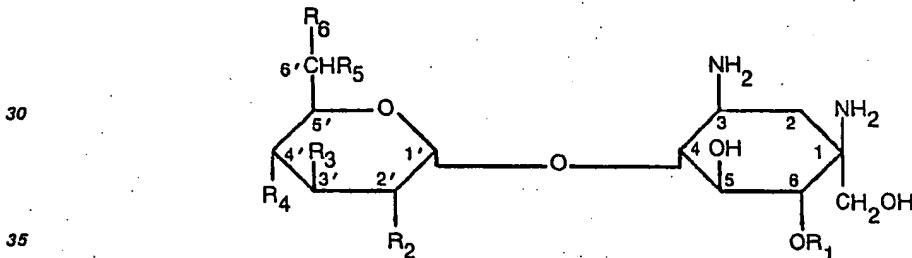
15 3. Un procédé tel que revendiqué à la revendication 2, dans lequel le sel d'addition d'acide est le pentachlorohydrate ou le sulfate.

16 4. Une composition pharmaceutique comprenant un composé préparé selon l'une quelconque des revendications 1 à 3 sous forme de base libre ou sous forme d'un sel d'addition d'acide de ce composé acceptable du point de vue chimiothérapeutique, ensemble avec un diluant ou véhicule acceptables du point de vue chimiothérapeutique.

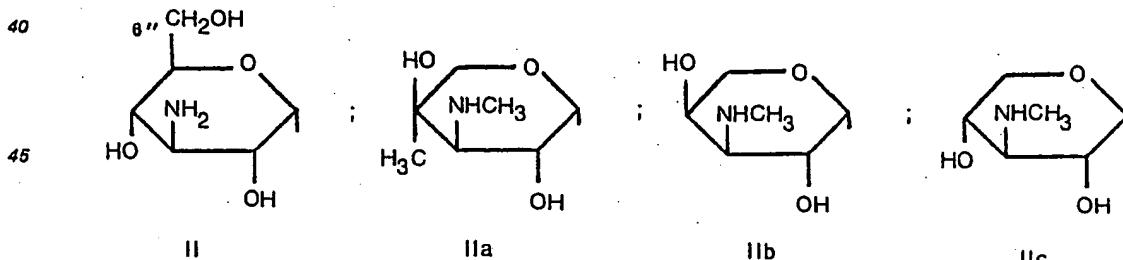
17 5. Un composé préparé selon l'une quelconque des revendications 1 à 3 sous forme de base libre ou sous forme d'un sel d'addition d'acide acceptable du point de vue chimiothérapeutique, pour l'utilisation comme médicament.

20 6. Un composé tel que préparé selon l'une quelconque des revendications 1 à 3, sous forme de base libre ou sous forme d'un sel d'addition d'acide acceptable du point de vue chimiothérapeutique, pour l'utilisation comme antibiotique à activité anti-bactérienne.

25 7. Un procédé de préparation d'une composition pharmaceutique comprenant l'admixtion d'un composé de formule



dans laquelle R₁ représente l'hydrogène ou un groupe de formule



50 R₂ représente un groupe hydroxy ou amino,
R₃ représente l'hydrogène ou un groupe hydroxy,
R₄ représente l'hydrogène ou un groupe hydroxy,
R₅ représente un groupe amino, méthylamino, diméthylamino ou, lorsque R₂ représente un groupe
55 amino, également un groupe hydroxy et

R₆ représente l'hydrogène ou un groupe méthyle, sous forme de base libre ou sous forme d'un sel d'additions d'acide de ce composé acceptable du point de vue chimiothérapeutique, avec un diluant ou véhicule acceptable du point de vue chimiothérapeutique.

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